claim 2 has been amended to recite methods for identifying cancer patients susceptible to arginine deprivation therapy comprising detecting the presence or absence of argininosuccinate synthetase ***protein*** in a cancerous tumor sample or in a non-cancerous sample of the corresponding tissue, rather than reciting detecting the presence or absence of argininosuccinate synthetase ***expression.*** Claims 6 to 8 and 27 have also been amended to replace the phrase "argininosuccinate synthetase *expression*" with the phrase "argininosuccinate synthetase *protein.*" Support for the amendments is found throughout the specification. No new matter has been added. Applicants respectfully submit that the objection has been obviated, and request withdrawal thereof.

B. Claim 6 has been objected to as drawn to non-elected subject matter for recitation of the phrase "peptide mass fingerprinting." The claim has been amended to delete the phrase, obviating the objection. Accordingly, Applicants respectfully request withdrawal thereof.

Alleged Indefiniteness

A. Claims 1 to 3, 6 to 9, 19 to 24, and 27 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the abbreviation "ASS." Claims 1, 2, 6 to 8 and 27 have been amended to replace "ASS" with "argininosuccinate synthetase," and claims 3, 8, 9, and 19 to 24 have been cancelled. Support for the amendments is found throughout the specification. No new matter has been added. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

B. Claim 8 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term "processed." Without conceding the correctness

of the rejection, and to advance prosecution, claim 8 has been cancelled, obviating the rejection. Accordingly, Applicants respectfully request withdrawal thereof.

C. Claim 27 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase "directed to." The Office Action asserts that "[i]t is not clear how the antibody is directed to ASS protein." (Office Action dated January 2, 2003, page 4). Without conceding the correctness of the assertion, and to advance prosecution by further clarifying the claimed subject matter, claim 27 has been amended to replace the phrase "an antibody directed to argininosuccinate synthetase protein" with the phrase "an antibody ***specific for*** argininosuccinate synthetase protein." Support for the amendment is found in the specification as filed at, for example, paragraph 42 on page 10. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

Alleged Lack of Enablement

A. Claims 1 to 3, 6 to 9, 19 to 24, and 27 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because the art is allegedly unpredictable with respect to whether argininosuccinate synthetase mRNA that is transcribed in a particular tumor tissue will also be translated in that tissue. Applicants respectfully traverse the rejection because the specification teaches that the expression of argininosuccinate synthetase in cancerous tumor samples is controlled at the level of transcription, rather than at the level of translation.

When making an enablement rejection, the Examiner bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). A specification that contains

a teaching of the manner and process of making and using an invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented ***must be taken as being in compliance with the enablement requirement*** unless there is a reason to doubt the objective truth of the statements contained therein. M.P.E.P. §2164.04.). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971).

The present specification teaches those skilled in the art that the expression of argininosuccinate synthetase in cancerous cells is controlled at the level of transcription, rather than at the level of translation. Example 2 describes experiments that revealed that argininosuccinate synthetase mRNA was not detected in melanoma and hepatoma cell lines, but was detected in breast adenocarcinoma, lymphoma, and lung carcinoma cell lines. The Example further teaches that ADI sensitive tumor cells were all deficient in mRNA encoding argininosuccinate synthetase. (See paragraph 98 of the specification as filed). Example 4 describes experiments demonstrating that human hepatocarcinoma cells did not contain detectable levels of argininosuccinate synthetase mRNA, while human colon and kidney cancer cells did. The example teaches that all of the human kidney cells tested were resistant to killing by ADI, while all of the hepatocarcinoma cells were sensitive to killing by ADI. (See paragraph 106 of the specification as filed). Finally, Example 3 describes experiments aimed at proving that the defect in arginine deiminase sensitive tumor cells is due to an inability of the cells to express argininosuccinate synthetase mRNA. The specification, therefore, teaches that arginine deiminase sensitive tumor cells are deficient in

argininosuccinate synthetase mRNA. Accordingly, the specification teaches that the expression of argininosuccinate synthetase in cancerous cells is controlled at the level of transcription, rather than at the level of translation. Consequently, assays that detect the presence or absence of argininosuccinate synthetase mRNA in cancerous tumor samples are predictive of whether argininosuccinate synthetase protein will be detected in the samples.

The Office Action asserts that assays for the detection of the argininosuccinate synthetase protein are not enabled by the specification because it is unpredictable whether argininosuccinate synthetase mRNA that is transcribed in a particular tumor tissue will be translated in that tissue:

> RNA assays cannot be predictably used to assess protein expression. It is unpredictable whether one can distinguish cancer cells that overexpress ASS RNA from cancer cells that do not express ASS RNA, i.e. cancer cells that are sensitive or not sensitive to ADI treatment, because it is unpredictable that cancer cells that overexpress ASS RNA would also express or overexpress ASS protein.

(Office Action dated January 2, 2003, page 6). As previously discussed, however, assays that detect the presence or absence of argininosuccinate synthetase mRNA in tumor cells ***are*** predictive of whether argininosuccinate synthetase protein will or will not be detected in the samples due to the fact that the expression of argininosuccinate synthetase in tumor cells is controlled at the level of transcription.

The Office Action cites numerous references in support of its assertion of unpredictability with respect to whether argininosuccinate synthetase mRNA is translated in particular tumor cells. All of the references, however, are directed to genes whose expression is regulated at the level of translation, rather than at the level of transcription. The references, therefore, do not constitute evidence that establishes a reason to doubt the truth of the teachings provided in the specification. Accordingly, Applicants respectfully submit that the

specification enables the full scope of the subject matter defined by the present claims, and respectfully request withdrawal of the rejection.

B. Claims 1 to 3, 6 to 9, 19 to 24, and 27 have also been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because no correlation allegedly exists between the expression of ASS mRNA in cells grown in tissue culture and the expression of argininosuccinate synthetase mRNA in cancer tissues *in vivo*. Applicants respectfully traverse the rejection because Applicants have demonstrated that a correlation exists between argininosuccinate synthetase expression in cancer cells grown in culture and the expression of the argininosuccinate synthetase protein in cancer tissues *in vivo*.

As explained in the attached Declaration of Mike Clark, an inventor of the subject matter claimed in the present application, Applicants have performed histochemical experiments in which monoclonal antibodies specific for the argininosuccinate synthetase protein were used to determine the frequency of argininosuccinate synthetase deficiency in various human cancers. A large number of human biopsy specimens were obtained and stained with a monoclonal antibody specific for the argininosuccinate synthetase protein. The experiments revealed that the incidence of argininosuccinate synthetase protein deficiency varied with the tumor type being tested. Melanoma, hepatocelular carcinoma, and sarcomas were the tumor types that were most frequently found to be deficient in the argininosuccinate synthetase protein, while the argininosuccinate synthetase protein was frequently detected in colon, lung, and breast biopsy specimens. As previously discussed, Examples 2 and 4 indicate that, in cancer cells grown in culture, argininosuccinate synthetase mRNA was not detected in melanoma and hepatoma, cells but was detected in colon, lung, and breast cells. Accordingly, Applicants have demonstrated that a correlation exists between argininosuccinate synthetase expression in cancerous cells grown in tissue culture

and argininosuccinate synthetase expression in cancer tissues *in vivo*. Applicants therefore respectfully request withdrawal of the rejection.

The Office Action also asserts that the specification is not enabling because it does not provide guidance or exemplification as to the susceptibility to treatment with arginine deiminase (ADI) of cancer patients who lack evidence of argininosuccinate synthetase expression in cancer tissues. Specifically, the Office Action asserts that "[b]ecause of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that a cancer patient having negative detection of ASS RNA in cancer tissues is susceptible to treatment with ADI." (Office Action dated January 2, 2003, page 10). Applicants respectfully submit that the Office Action has failed to meet its burden in establishing lack of enablement on this ground.

As previously discussed, a specification that contains a teaching of the manner and process of making and using an invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented ***must be taken as being in compliance with the enablement requirement*** unless there is a reason to doubt the objective truth of the statements contained therein. In addition, the Patent Office must explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and must back up its assertions with acceptable evidence or reasoning that is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971).

The Office Action has failed to offer any ***specific*** reasons to doubt the objective truth of the teachings provided in the specification with respect to the susceptibility to treatment with ADI of cancer patients who lack evidence of argininosuccinate synthetase expression in cancer tissues. The Office Action has merely offered general statements as to the alleged unpredictability of anticancer drug discovery and has cited numerous references relating to

the treatment of cancer, none of which address, or even mention, methods for identifying cancer patients susceptible to arginine deprivation therapy. Accordingly, the Office Action has failed to support its assertions with acceptable evidence or reasoning that is ***specific*** to the claimed methods. The Office Action has, therefore, failed to provide credible evidence or reasoning that is inconsistent with the teachings made in the specification, and has thus failed to meet its burden in establishing lack of enablement.[1]

Applicants respectfully submit that the specification enables those skilled in the art to make and use the full scope of the claimed subject matter without undue experimentation, and accordingly, respectfully request withdrawal of the rejection.

Alleged Lack of Enablement - Scope

A. Claims 1 to 3, 6 to 9, 19 to 24, and 27 have been rejected under 35 U.S.C. § 112, first paragraph because the specification is allegedly not commensurate in scope with the claims. Applicants respectfully traverse the rejection because the specification enables those skilled in the art to make and use the full scope of the subject matter defined by the claims without undue experimentation.

The Office Action asserts that since the specification teaches that argininosuccinate synthetase mRNA was not detected in all types of cancers, it is unpredictable whether argininosuccinate synthetase will be detected in any cancer, including sarcoma. Based on this premise, the Office Action concludes that the specification enables methods for determining if a cancer patient is susceptible to arginine deprivation therapy, where the patient has hepatoma, melanoma, or breast cancer, but does not enable methods for

[1] Moreover, the Office Action's statement that those skilled in the art would not accept the assertion that a cancer patient having negative detection of ASS RNA in cancer tissues is susceptible to treatment with ADI highlights the novelty and nonobviousness of Applicants' inventions.

determining if a cancer patient is susceptible to arginine deprivation therapy, where the patient has any type of cancer or sarcoma.

Applicants respectfully disagree and point out that the finding that argininosuccinate synthetase is not expressed in all types of cancers is what led to the development of the claimed subject matter, *i.e.*, to the development of methods for determining which cancer patients are amenable to treatment with arginine deprivation therapy. The specification teaches that the claimed methods can and should be applied to cancer patients with all types of cancers, including sarcomas, to determine if the particular type of cancer from which the patient suffers should be treated with ADI.

The specification teaches that 60% of the tested human sarcomas were found to be sensitive to ADI killing. Accordingly, if a patient were diagnosed with sarcoma, the patient should be tested to determine if the sarcoma is amenable to treatment with ADI prior to commencement of arginine deprivation therapy. That is, since not all sarcomas are deficient in argininosuccinate synthetase, the patient should be tested to determine if argininosuccinate synthetase is present in the patient's cancerous tissues prior to beginning arginine deprivation therapy. The same holds true of patients that suffer from *all types* of cancers. Accordingly, as taught in the specification, the claimed methods are applicable to, and can be used for, patients that suffer from *all types* of cancers, and not just certain cancers that are known to be deficient in argininosuccinate synthetase, to allow clinicians to determine which cancer patients should be treated with ADI.

The specification enables those of skill in the art to practice the claimed methods using cancerous samples from patients that suffer from ***all types of cancers***, and not just samples from patients that suffer from hepatoma, melanoma, or breast cancer. Notably, the Office Action has failed to offer any credible evidence or reasoning to the contrary.

Accordingly, the evidence of record fails to demonstrate that those of skill in the art would be unable to practice full scope of the claimed methods without undue experimentation, and Applicants respectfully request withdrawal of the rejection.

B. Claims 1 to 3, 6 to 9, 19 to 24, and 27 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that the specification is enabling for detecting the presence or absence of argininosuccinate synthetase protein in ***cancer*** samples from patients, but is not enabling for detecting the presence or absence of argininosuccinate synthetase protein in ***tumor*** samples from patients. Without conceding the correctness of the assertion, and to advance prosecution by further clarifying the claimed subject matter, claims 1, 2, 8, and 27 have been amended to recite "cancerous tumor sample" rather than "tumor sample." Claims 3, 9, and 19 to 24 have been cancelled. Support for the amendments is found throughout the specification. No new matter has been added. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

C. Claim 2 has been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that the specification is enabling for methods of identifying cancer patients susceptible to arginine deprivation therapy comprising detecting in a cancer sample, and a non-cancerous sample from the corresponding tissue, the presence or absence of argininosuccinate synthetase protein, but is not enabling for methods of identifying cancer patients susceptible to arginine deprivation therapy comprising detecting in a cancer sample and a "non-cancerous sample" the presence or absence of argininosuccinate synthetase protein. Without conceding the correctness of the assertion, and to advance prosecution by further clarifying the claimed subject matter, claim 2 has been amended to recite "a non-cancerous sample ***of the corresponding tissue*** from the cancer

patient." Support for the amendment is found throughout the specification. No new matter has been added. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

D. Claim 27 has been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that the specification enables methods of detecting the presence or absence of argininosuccinate synthetase protein using an antibody that specifically binds to the argininosuccinate synthetase protein, but does not enable methods of detecting the presence or absence of argininosuccinate synthetase protein using an antibody that is "directed to" the argininosuccinate synthetase protein or "portion thereof." As previously discussed, claim 27 has been amended to replace the phrase "an antibody directed to argininosuccinate synthetase protein" with the phrase "an antibody ***specific for*** argininosuccinate synthetase protein." Support for the amendment is found in the specification as filed at, for example, paragraph 42 on page 10. Applicants respectfully submit that the rejection has been obviated, and request withdrawal thereof.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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Date: May 9, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claims 1, 2, 6, 7 and 27 have been amended as follows.

1. (Amended) A method for identifying a cancer patient susceptible to arginine deprivation therapy comprising the steps:

a) obtaining a cancerous tumor sample from the cancer patient; and

b) detecting the presence or absence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said cancerous tumor sample, wherein the absence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said cancerous tumor sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy and the presence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

2. (Amended) The method of claim 1 wherein prior to, simultaneous with, or after testing the cancerous tumor sample, the method further comprises the steps of:

c) obtaining a non-cancerous sample of the corresponding tissue from the cancer patient; and

d) detecting the presence or absence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said non-cancerous sample, wherein the absence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said non-cancerous sample and the absence of [evidence of ASS] argininosuccinate synthetase [expression]

protein in said cancerous tumor sample is indicative of a cancer patient who is not a good candidate for arginine deprivation therapy, wherein the presence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said non-cancerous sample and the absence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said cancerous tumor sample is indicative of a cancer patient who is a good candidate for arginine deprivation therapy, and wherein the presence of [evidence of ASS] argininosuccinate synthetase [expression] protein in said cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

6. (Amended) The method of claim 1 wherein the presence or absence of [evidence of ASS] argininosuccinate synthetase [expression] protein is detected using a technique selected from the group consisting of Western blotting, ELISA, enzyme assays, slot blotting, [peptide mass fingerprinting,] electrophoresis, and immunohistochemistry.

7. (Amended) The method of claim 1 wherein the presence or absence of [evidence of ASS] argininosuccinate synthetase [expression] protein is detected using ELISA.

27. (Amended) The method of claim 1 wherein [said evidence of ASS] argininosuccinate synthetase [expression] protein in said cancerous tumor sample is detected comprising the steps of:

a) contacting the cancerous tumor sample of the cancer patient with an antibody [directed to] specific for an [ASS] argininosuccinate synthetase protein, or portion thereof; and

b) detecting binding of the antibody to said [ASS] argininosuccinate synthetase protein, or portion thereof, in said cancerous tumor sample wherein the absence of binding of the antibody to said [ASS] argininosuccinate synthetase protein is indicative of a cancer patient who is a candidate for arginine deprivation therapy and the presence of binding of the antibody to said [ASS] argininosuccinate synthetase protein in said cancerous tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

Claims 3 to 5, 8 to 26, and 28 to 30 have been cancelled.

New claims 31 to 36 have been added.